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MERCK AND CO INC
P O BOX 2000
RAHWAY, NJ 070650907

EXAMINER
LI, QIAN J

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/642,405	Applicant(s) NEEPER ET AL.	
	Examiner Janice Li	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

Claims 1-30 are pending in the application and under current examination.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention

is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

These claims recite "a HPV protein which has reduced protein function as compared to wild-type protein, but which maintains immunogenicity", "the polynucleotide sequence comprising codons optimized for expression in a human host", and the claims embrace at least 8 different HPV proteins, numerous mutated form of a HPV proteins from at least 14 different types of human papillomavirus.

The specification teaches "In accordance with this invention, HPV gene segments were converted to sequences having identical translated sequences but with alternative codon usages as defined by Lathe", the specification list general rules of selecting such codon, and teach, "it has been found that the use of alternative codons encoding the same protein sequence may remove the constraints on expression of HPV proteins by human cell".

The claim recitations "a HPV protein which has reduced protein function as compared to wild-type protein, but which maintains immunogenicity", "the polynucleotide sequence comprising codons optimized for expression in a human host" are obvious generic to a considerable number of proteins and polynucleotides, varying in the codon

usages. The specification fails to provide an adequate description to teach the sequences and characteristics of all possible or representative alternate codons that would be desirable for expression in human, the identifying characteristics and the structure-function relationship of the alternative codons for the broad class of proteins and polypeptides with regard to their function as optimized for expression in humans, and accordingly does not provide a reasonable guide for those seeking to practice the invention.

An adequate written description for a polypeptide or a polynucleotide requires more than a mere statement that it is part of the invention; what is required is a description of the chemical structures and physical properties of the codons, the proteins, and polynucleotides themselves. It is not sufficient to define the agents solely by its principal biological property, i.e. "a HPV protein which has reduced protein function as compared to wild-type protein, but which maintains immunogenicity", and it is not sufficient to define the polynucleotides solely by its principal biological property, i.e. "the sequence comprising codons optimized for expression in a human host", because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any agent with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all proteins and polynucleotides that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and

Regents of the Univ. Calif. v. Eli Lilly & Co., 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific chemical and physical properties of a chemical, or the sequences of a protein and nucleic acids, which provide the means for practicing the invention. The court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of *all* or representative species of the genus. Therefore, only the described sequences SEQ ID Nos: 1-4 meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inducing an immune response to HPV in mice

using a codon optimized polynucleotides encoding HPV proteins, wherein the polynucleotide is selected from the group consisting of SEQ ID Nos: 1-4, does not reasonably provide enablement for inducing a protective immune response to HPV in *humans* using the polynucleotide selected from the group consisting of SEQ ID Nos: 1-4, and it does not reasonably provide enablement for using any protein having an alterative codon usage and any mutated form of a HPV protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

As summarized in the specification, determination of the proper protein codons that would generate a protein that "*has reduced protein function as compared to wild-type protein, but which maintains immunogenicity or* that are *"optimized for expression in a human host*", requires 1) identification of placement of codons for proper OPF, 2) comparing wild type codon for observed frequency of use by human genes, 3) replacing the wild codon with an optimal codon for high expression in human cells as necessary, 4) repeating the procedure until the entire gene segment has been replaced, 5) inspect

new gene sequence to eliminate other undesired sequences generated by these codon replacements, and 6) assemble and test the new gene segment for improved expression. Considering that claims embrace 8 natural occurring proteins from 14 different types of HPVs, and each of the proteins comprising about 600 amino acid residuals, and uncountable numbers of mutants, the selection of which has reduced protein function as compared to wild-type protein, but which maintains immunogenicity, thus, it would require extensive amount of experimentation. Furthermore, the functional changes indicate certain structural changes of these proteins, no art of record nor the specification teaches which codon, which amino acid, and how much codon changes could the protein tolerate without abrogating the *immunogenicity of* HPV proteins. The claims and the specification essentially do not place any limit on the number of alternative codons that could be substituted, thus the scope of the claims includes numerous structural variants, and a genus of DNA molecules encoding such. Because it is the three-dimensional structure of a polypeptide that allows the protein to function and serve as immunogenic epitope, which requires proper dimerization and interaction with antibodies and cell receptors, the function of the polypeptide could be abolished even with substitution of only one amino acid of the peptide encoded by said nucleotide sequence. *Bowie et al* (Science 1990 Mar; 247:1306-10) teach that certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or none at all (page 1306, column 2). *Rudinger* (Peptide Hormones 1976; June;pages 1-7) teaches the relationship of sequence components and the peptide hormone function "THE

SIGNIFICANCE OF PARTICULAR AMINO ACIDS AND SEQUENCES FOR DIFFERENT ASPECTS OF BIOLOGICAL ACTIVITY CANNOT BE PREDICTED *A PRIORI* BUT MUST BE DETERMINED FROM CASE TO CASE BY PAINSTAKING EXPERIMENTAL STUDY." (last paragraph of text on page 6). Determination of the effects of particular codon modifications is not predictable until they are actually made and used, hence resulting in a trial and error situation. Therefore, the general knowledge and levels of skill in the art do not supplement the omitted description, because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of all possible polypeptides and polynucleotides, SEQ ID Nos: 1-4 alone are insufficient to describe the characteristics of the genus of nucleotide sequences that are optimized for expression in a human host. One can not predictively extrapolate the teachings of the specification to the scope of the claims because the skilled artisan cannot envision the detailed structure of polynucleotides encompassed by these claims and whether the resulting polypeptide can serve as a HSV protein which has reduced protein function as compared to wild-type protein, but which maintains immunogenicity. Therefore, the skilled artisan could not practice the invention without undue experimentation.

The claimed invention additionally reads on therapeutic methods. For example, claim 19 recites "an adenoviral vaccine", claim 22 recites "a vaccine plasmid", and claims 26 and 27 recite "a method for inducing an immune response in a vertebrate, wherein the vertebrate is a human". These claims clearly or implicitly state the intended use of the composition and methods. With respect to claim breadth, the standard under

35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. "WHEN A COMPOUND OR COMPOSITION CLAIM IS LIMITED BY A PARTICULAR USE, ENABLEMENT OF THAT CLAIM SHOULD BE EVALUATED BASED ON THAT USE". (MPEP 2164.01c) When analyzing the enabled scope of the claims, the intended use is to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. "A vaccine composition" is defined, as a composition for therapeutic use, to prevent, alleviate, treat, or cure a disease within the animal to which the substance is administered, therefore, will be evaluated by the standard. As such, the broadest reasonable interpretation of the claimed invention properly encompasses genetic vaccination for human papillomavirus-associated diseases, therefore, the claims will be evaluated by that standard.

In view of the guidance provided, the specification teaches to immunize balb/c mice with a V1Jns-E2 DNA followed by subcutaneous injection of tumor cells, tumor growth was inhibited in the immunized group. However, the specification fails to teach the association between the effects of an artificial animal model and prophylactic and treatment in humans.

In view of the state of the art in gene therapy for human, *McCluskie et al* (Mol Med 1999 May;5:287-300) TEACH "UNFORTUNATELY, THE PROMISING RESULTS IN ANIMAL MODELS HAVE NOT BEEN REALIZED IN HUMAN TRIALS AND CONSIDERABLE EFFORT IS NOW BEING FOCUSED AT UNDERSTANDING THIS DIFFERENCE AND DEVELOPING WAYS OF IMPROVING THE EFFICACY OF DNA VACCINES." (See 1st paragraph of the introduction) "HOWEVER, THE RESULTS IN MICE WERE NOT ALWAYS PREDICTIVE OF THOSE IN MONKEYS AND THIS IS LIKELY TRUE FOR HUMANS AS WELL. OPTIMAL DOSE AND IMMUNIZATION SCHEDULE WILL MOST LIKELY VARY

BETWEEN SPECIES. IT IS NOT CLEAR WHETHER RESULTS IN NON-HUMAN PRIMATES WILL BE PREDICTIVE OF RESULTS IN HUMANS, THUS ADDITIONAL STUDIES ARE REQUIRED." (See abstract) *Orkin et al.* (NIH Report, 1995 Dec) reviews the infant state of the art of gene therapy from before the instant invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; and 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints (pages 1-2). Although the reference is ages old, the general status of gene therapy art has not significantly changed. *Moingeon et al* (Trends Immunol 2002 Apr;23:173-5) teach, "THE DISCOVERY OF NEW ANTIGENS ABLE TO ELICIT PROTECTIVE IMMUNE RESPONSES AGAINST INFECTIOUS PATHOGENS REMAINS ONE OF THE MOST IMPORTANT CHALLENGES IN VACCINOLOGY" (page 173, left column). "THE NEED FOR ANTIGEN-PRESENTATION PLATFORMS AND/OR ANTIGEN FORMULATIONS ELICITING POTENT T-CELL RESPONSES AND MUCOSAL IMMUNITY IN HUMANS, AS WELL AS THE POOR PREDICTIVE VALUE OF ANIMAL MODELS, WERE EMPHASIZED ALSO". (paragraph bridging pages 174 and 175) Further, in light of the specification, the claims also embrace vaccination for cancers. Although HPV is known for its tumor-causing effect, the virus is not the sole cause in the development of cancer in humans, the host immune state also plays an important role. *Bodey et al* (Anticancer Res 2000;20:2665-76) review cancer vaccines in cancer

immunotherapy, "THE THEORETICAL BASIS FOR ALL OF THESE APPROACHES IS VERY WELL FOUNDED. ANIMAL MODELS, ALBEIT HIGHLY ARTIFICIAL, HAVE YIELDED PROMISING RESULTS. CLINICAL TRIALS IN HUMANS, HOWEVER, HAVE BEEN SOMEWHAT DISAPPOINTING...", "THE CANCER VACCINE APPROACH TO THERAPY IS BASED ON THE NOTION THAT THE IMMUNE SYSTEM COULD POSSIBLY MOUNT A REJECTION STRENGTH RESPONSE AGAINST THE NEOPLASTICALLY TRANSFORMED CELL CONGLOMERATE. HOWEVER, DUE TO THE LOW IMMUNOGENICITY OF TUMOR ASSOCIATED ANTIGENS, DOWNREGULATION OF MHC MOLECULES, THE LACK OF ADEQUATE COSTIMULATORY MOLECULE EXPRESSION, SECRETION OF IMMUNE INHIBITORY CYTOKINES, ETC., SUCH EXPECTATION ARE RARELY FULFILLED...FAULTY ANTIGEN PRESENTATION WHICH COULD RESULT IN TOLERANCE INDUCTION TO THE ANTIGENS CONTAINED WITHIN THE VACCINE, AND SUBSEQUENT RAPID TUMOR PROGRESSION." (page 2665, column one). Thus, it is evident that at the time of the invention, the skilled artisan in the relevant art, while acknowledging the significant potential of immunotherapy for cancer and HPV-associated diseases, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such therapeutic regimen. Although the instant specification provides ex vivo and in vivo data in a mouse tumor model to illustrate a potential therapeutic use of the claimed compositions and methods, it is not enabled for its full scope because the art-recognized barriers in achieving successful cancer immunotherapy and differences in immune responses between a mouse tumor model and cancer patients.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation

would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for identifying the polynucleotide sequences comprising alternate codons optimized for expression in humans, for achieving successful HPV vaccination in humans, the lack of direction provided by the specification, and the breadth of the claims directed to the use of numerous combinations of codon optimized therapeutic genes/vectors, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 8-10, 12, 13, 16, 17, and 24-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims are vague and indefinite because claims 1 and 30 recite "a HPV protein which has reduced protein function as compared to wild-type protein", it is unclear what "reduced protein function" the claims refer to, thus, the metes and bounds of the claims are unclear.

Claims 24-30 are incomplete. The claims are directed to a method for inducing an immune response in a vertebrate, however, it is unclear how mere introduction of the polynucleotide relates to inducing an immune response or how cell expression relates to making a protein, and how the polynucleotides are delivered. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-6, 22, and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by *Hofmann et al* (US 6,159,729).

Claims are drawn to a polynucleotide comprising a sequence encoding a human papillomavirus (HPV) protein, selected from the group consisting of L1, L2, and E1, E2,

E4-E7, preferably L1 which is selected from a HPV from the group consisting of different types of HPV, e.g. HPV11 and HPV16, wherein the polynucleotide is DNA. Claim 22 is drawn to a plasmid comprising an expression cassette comprising said polynucleotide operably linked to a promoter. Claim 30 is drawn to a method of making a HPV protein comprising expressing in a host cell a polynucleotide encoding a HPV protein.

Hofmann et al teach a polynucleotide comprising a sequence encoding a human HPV11 L1 protein (claim 1) in an expression vector (claim 5), wherein the vector is a plasmid (see example 4) comprising an expression cassette, wherein the protein could be extracted from different type of HPVs, such as HPV16 (column 22, line 47). And the vector could be used to express HPV protein in a host cell (Example 6). Thus, *Hofmann et al* anticipate the instant claims.

Please note that the claim recitations "which has reduced protein function as compared to wild-type protein", "the polynucleotide sequence comprising codons optimized for expression in a human host" have not been given patentable weight in the instant and following rejections because the intended use for immunogenicity does little toward defining structure of the claimed antigen. Rather, polynucleotide and polypeptide sequences are relied upon for structural determination.

Claims 1-5, 22, and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by *Joyce et al* (US 5,820,870).

Joyce et al teach a polynucleotide comprising a sequence encoding a human HPV18 L1 and L2 protein in an expression vector (examples 1-4), wherein the vector is a plasmid comprising an expression cassette. And the vector could be used to express HPV protein in a host cell (Example 6).Thus, *Joyce et al* anticipate the instant claims.

Claims 1-6, 8-10, 12, 13, 16, 17, 22, and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by *Whittle et al* (US 6,123,948).

Whittle et al teach a polynucleotide comprising a sequence encoding a fusion protein of HPV, an example of such is the fusion of HPV6 L2 and E7 in an expression vector (example 7, for example), wherein the vector is a plasmid comprising an expression cassette. *Whittle et al* also teach that the antigenic determinants selected from the L1, L2, and E1-E7 could be used as such fusion partners and different types of HPVs could be the source of extraction, such as HPV6, 11, 16, and 18 (paragraph bridging columns 3-4), and the vector could be used for making HPV proteins and fusion proteins. Thus, *Whittle et al* anticipate the instant claims.

Claims 1-6, 19, 20, 21, and 26 are rejected under 35 U.S.C. 102(e) as being anticipated by *Ertl et al* (US 6,019,978).

Claims 19, 20, are drawn to an adenoviral vector comprising an adenoviral genome with a deletion in the E1 region and an insertion in the E1 region, wherein the insertion comprising a polynucleotide encoding a HPV protein selected from the group consisting of L1, E1, E2 and E7, operably linked to a promoter, wherein the E3 region of the Adv was also deleted. Claim 21 is drawn to a vector comprising a plasmid portion and an adenoviral portion comprising a polynucleotide encoding a HPV protein selected from the group consisting of L1, E1, E2 and E7, operably linked to a promoter. Claim 26 is drawn to a method for inducing immune responses in a vertebrate, comprising

introducing the recited polynucleotide vectors into the tissue of the vertebrate in two separate doses.

Ertl et al teach an adenoviral vector comprising complete or partial deletions in E1 and E3 region (abstract), the vector comprising a portion of a plasmid and a portion of adenovirus genome (figures, paragraph bridging columns 7 & 8) and a CMV promoter operably linked to polynucleotide coding region, wherein the encoded sequences in the E1 deletion site could be HPV L1, E6, and E7 (claims 2-4), wherein the vector could be used to induce a protective immune response against HPV (claims 1-6) via single or multiple dosing regimen (Example 3, for example) via subcutaneous, oral, intranasal, intratracheal routes. Therefore, *Ertl et al* anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 8-10, 12, 13, 16, 17, 19-26, 28, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Ertl et al* ((US 6,019,978) as applied to claims 1-6, 19, 20, 21, and 26 above, and *Whittle et al* (US 6,123,948) as applied to claims 1-6, 8-10, 12, 13, 16, 17, 22, and 30, and further in view of *Donnelly et al* (J Infect Diseases 1996;713:314-20).

Claims 22 and 23 are drawn to a plasmid comprising an expression cassette comprising said polynucleotide operably linked to a promoter, wherein the plasmid is V1Js. Claims 24 and 25 are drawn to a method for inducing immune response in a vertebrate which comprises introducing between 1ng and 100mg of the polynucleotide into the tissue of the vertebrate, wherein the viral particles are 10^{11}-10^{12}. Claim 28 is drawn to a method for inducing immune response in a vertebrate using first plasmid vector and then Adv vector encoding HPV proteins.

Ertl et al teach an adenoviral vector comprising complete or partial deletions in E1 and E3 region (abstract), the vector comprising a portion of a plasmid and a portion of adenovirus genome (figures, paragraph bridging columns 7 & 8) and a CMV promoter operably linked to polynucleotide coding region, wherein the encoded sequences could be HPV L1, E6, and E7 (claims 2-4), wherein the vector could be used to induce a protective immune response against HPV (claims 1-6) in mice by single- or multiple-dosing regimen (Example 3, for example) via subcutaneous, oral, intranasal, and intratracheal routes, they teach to use viral titers between 10^4-10^6. *Ertl et al* do not teach immunization with a plasmid vector encoding HPV proteins, or a V1Js plasmid.

Whittle et al teach a polynucleotide comprising a sequence encoding a fusion protein HPV6 L2 and E7 in an expression vector (example 7, for example), wherein the vector is a plasmid comprising an expression cassette. *Whittle et al* also teach that the antigenic determinants selected from the L1, L2, and E1-E7 could be used as such fusion partners and different types of HPVs could be the source of extraction, such as HPV6, 11, 16, and 18 (paragraph bridging columns 3-4), and the vector could be used

for making HPV proteins and fusion proteins. They teach that the HPV polypeptides provided are useful and effective in eliciting HPV-specific immune response e.g. as vaccines for prophylaxis or therapy of papillomavirus-associated conditions (column 6, lines 19-23). *Whittle et al* do not teach nucleic acid immunizations.

Donnelly et al teach a polynucleotide comprising a sequence encoding a cottontail rabbit papillomavirs HPV11 L1 and L2 protein in an expression vector V1J derivative V1Jns (M & M section), *Donnelly et al* introduce the vector to a rabbit model for HSV via intramuscular injection at an arbitrary doses between 60 μg-1mg, and observe a protective effect against subsequent CRPV challenge. *Donnelly et al* teach advantages using DNA vaccination over certain conventional vaccine approaches, "DNA IMMUNIZATION SHARES WITH RECOMBINANT AND SUBUNIT APPROACHES THE ABILITY TO USE VIRAL GENE SEQUENCES DERIVED BY PCR DIRECTLY FROM HUMAN CLINICAL SPECIMENS", "DELIVERY OF A COMBINATION OF CAPSID PROTEINS AS PLASMID DNAS WOULD SIMPLIFY THE PREPARATION OF A MULTIVALENT HPV VACCINE", AND "IMMUNIZATION WITH DNA IS AN EFFECTIVE MEANS OF INDUCING CELLULAR IMMUNITY" (pages 318-9). They teach that the results suggest that a DNA vaccine merits consideration as a potential alternative for the vaccination of human s against HPV. *Donnelly et al* use CRPV rather than HPV in their experiments.

Evidently, to induce a protective immune response to papilloma virus in animal models using adenovirus or plasmid vectors such as V1Js encoding papilloma viral proteins and the appropriate dosing regimen is well-know in the art as taught by *Ertl et al, and Donnelly et al*; selecting L1, L2, E2 and E7 or mutating among these proteins as preferred immunogenic epitope is also known in the art as taught by *Whittle* and *Ertl et al*. Thus, it would have been obvious to one of ordinary skill in the art at the time the

invention was made to modify the methods taught by *Ertl et al, Donnelly, and Whittle et al*, by selecting or combining an immunogenic protein of interest and using the vectors of interest, as taught by *Ertl et al, Donnelly, and Whittle et al,* to induce an immune response to HPV in an animal model with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the method because the advantages using DNA vaccination and proven effectiveness of the vectors taught by *Ertl et al, and Donnelly et al* in eliciting a protective immune response. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim Objections

Claims 7, 11, 14, 15, and 18 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
May 31, 2002

JAMES KETTER
PRIMARY EXAMINER